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Group 125

#19
1 of 3
JRP
10/4/88

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	)	
	)	
Nicholas S. BODOR	)	Group Art Unit: 125
	)	
Serial No.: 807,034	)	Examiner: Joseph A. Lipovsky
	)	
Filed: December 9, 1985	)	
	)	
For: SOFT STEROIDS HAVING ANTI-INFLAMMATORY ACTIVITY	)	

89-2082

APPELLANT'S BRIEF ON APPEAL
UNDER 37 C.F.R. §1.192a

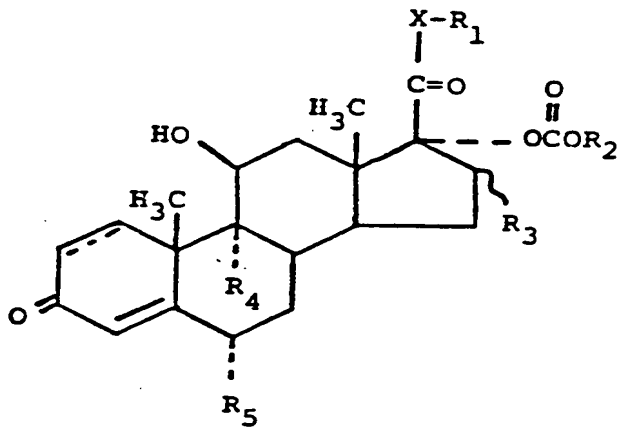
I. INTRODUCTION:

This is an appeal from the Examiner's Final Rejection dated November 24, 1987, finally rejecting claims 1-45, 56-63 and 65-117. Claims 46-51 have been objected to, and claim 118 has been allowed. This brief is submitted in triplicate. A check in the amount of the required appeal fee [$130.00] is attached.

II. THE CLAIMS ON APPEAL:

1. A compound selected from the group consisting of:

(a) a compound of the formula



(I)

wherein:

R_1 is C_1-C_{10} alkyl; C_2-C_{10} (monohydroxy or polyhydroxy)alkyl; C_1-C_{10} (monohalo or polyhalo)alkyl; or $-CH_2COOR_6$ wherein R_6 is unsubstituted or substituted C_1-C_{10} alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl or C_2-C_{10} alkenyl, the substituents being selected from the group consisting of halo, lower alkoxy, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl,

$-NHC-(C_1-C_{10}$ alkyl) and $-OC-(C_1-C_{10}$ alkyl), or R_6 is unsubstituted or substituted phenyl or benzyl, the substituents being selected from the group consisting of lower alkyl, lower alkoxy, halo, carbamoyl, lower alkoxycarbonyl, lower alkanoyloxy, lower haloalkyl, mono(lower alkyl)amino, di(lower alkyl)amino, mono(lower alkyl)carbamoyl, di(lower alkyl)carbamoyl, lower alkylthio, lower alkylsulfinyl and lower alkylsulfonyl; or R_1 is $-CH_2CONR_7R_8$ wherein R_7 and R_8, which can be the same or different, are each hydrogen, lower alkyl, C_3-C_8 cycloalkyl, phenyl or benzyl, or R_7 and R_8 are combined such that $-NR_7R_8$ represents the residue of a saturated monocyclic secondary amine; or R_1 is unsubstituted or substituted phenyl or benzyl, the substituents being selected from the group of phenyl and benzyl substituents defined hereinabove with respect to R_6; or R_1 is $-CH(R_9)-Y-$(lower alkyl) wherein Y is -S-, -SO-, $-SO_2-$ or -O- and R_9 is hydrogen, lower alkyl or phenyl, or R_9 and the lower alkyl group adjacent to Y are combined so that R_1 is a cyclic system of the type $-CH(-alkylene-)-Y$ wherein Y is defined as above and the alkylene group contains 3 to 10 carbon atoms, of which at least 3 and no more than 6 are ring atoms; or R_1 is $-CH(R_{10})-OCR_6$ wherein R_6 is defined as hereinabove and R_{10} is hydrogen, lower alkyl, phenyl or halophenyl;

R_2 is unsubstituted or substituted C_1-C_{10} alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl or C_2-C_{10} alkenyl, the substituents being selected from the group consisting of halo, lower alkoxy, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, $-NHC-(C_1-C_{10}$ alkyl) and $-OC-(C_1-C_{10}$ alkyl), or R_2 is unsubstituted or substituted phenyl or benzyl, the substituents being selected from the group consisting of lower alkyl, lower alkoxy, halo, carbamoyl, lower alkoxycarbonyl, lower

alkanoyloxy, lower haloalkyl, mono(lower alkyl)amino, di(lower alkyl)amino, mono(lower alkyl)carbamoyl, di(lower alkyl)carbamoyl, lower alkylthio, lower alkylsulfinyl and lower alkylsulfonyl;

R_3 is hydrogen, α-hydroxy, β-hydroxy, α-methyl, β-methyl, $=CH_2$, or α- or β-$OCOR_2$ wherein R_2 is identical to R_2 as defined hereinabove;

R_4 is hydrogen, fluoro or chloro;

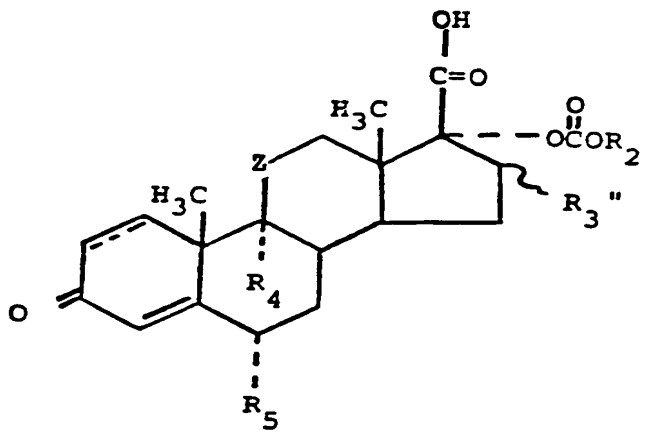
R_5 is hydrogen, fluoro, chloro or methyl;

X is -O- or -S-;

and the dotted line in ring A indicates that the 1,2 linkage is saturated or unsaturated;

(b) a quaternary ammonium salt of a compound of formula (I) wherein at least one of R_1 and R_2 is a halo-substituted alkyl group;

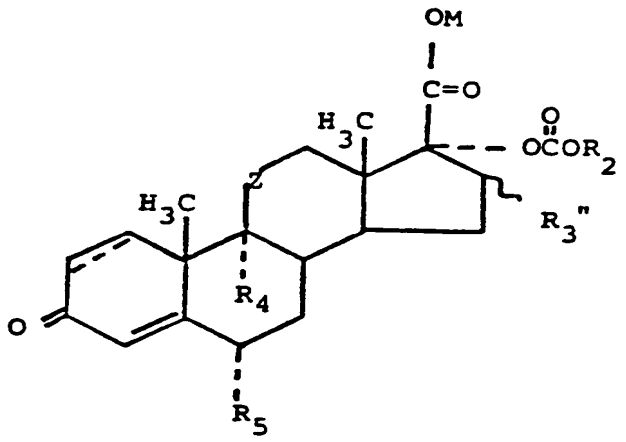
(c) a compound of the formula



(III)

wherein R_2, R_4, R_5, and the dotted line in ring A are as defined in (a) above, Z is carbonyl or β-hydroxymethylene and R_3" is hydrogen, α-methyl, β-methyl, $=CH_2$ or α- or β-$OCOR_2$ wherein R_2 is identical to R_2 above;

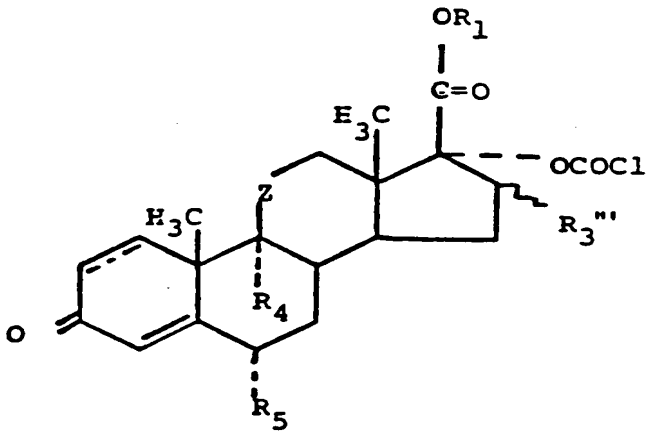
(d) a compound of the formula



(IV)

wherein M is alkali metal, thallium, alkaline earth metal/2 or NH_4 and R_2, $R_3"$, R_4, R_5, Z and the dotted line in ring A are as defined in (a) and (c) above;

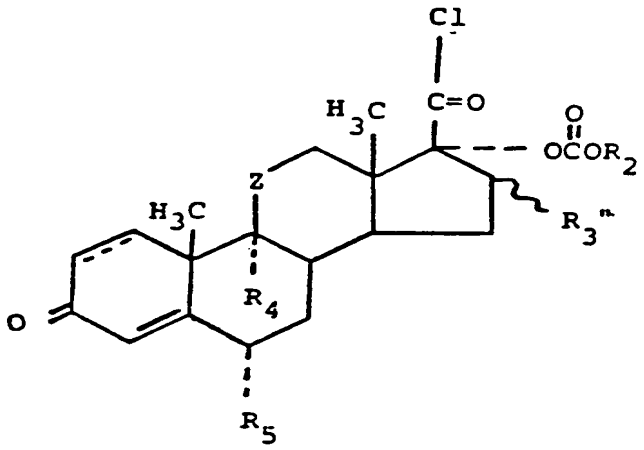
(e) a compound of the formula



(VII)

wherein R_3''' is hydrogen, α-methyl, β-methyl, α-OCOCl or β-OCOCl, and R_1, R_4, R_5, Z and the dotted line in ring A are as defined in (a) and (c) above;

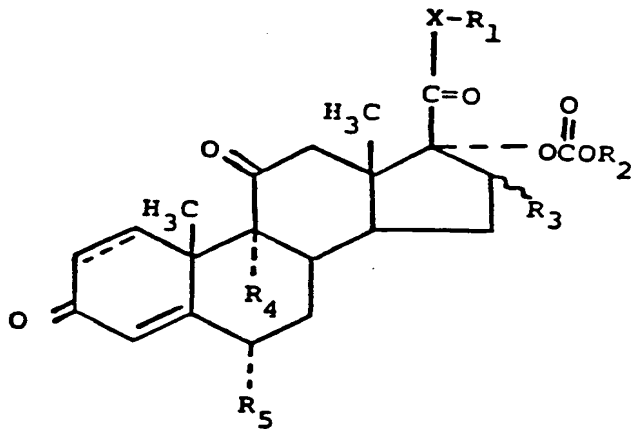
(f) a compound of the formula



(VIII)

wherein R_2, R_3'', R_4, R_5, Z and the dotted line in ring A are as defined in (a) and (c) above; and

(g) a compound of the formula

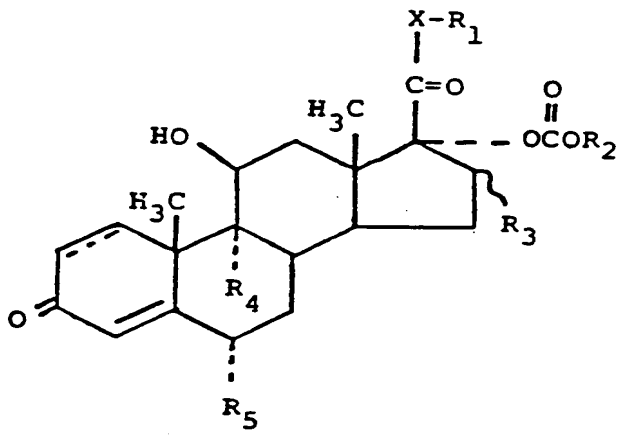


(IX)

wherein R_1, R_2, R_3, R_4, R_5, X and the dotted line in ring A are as defined in (a) above.

2. A compound selected from the group consisting of:

(a) a compound of the formula



(I)

wherein:

R_1 is C_1-C_6 alkyl; C_1-C_6 (monohalo or polyhalo)alkyl; $-CH_2COOR_6$ wherein R_6 is C_1-C_6 alkyl; $-CH_2-Y-(C_1-C_6$ alkyl) wherein Y is -S-, -SO-, $-SO_2-$ or -O-; or $-CH_2OCR_6'$ wherein R_6' is C_1-C_6 or phenyl;

R_2 is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, phenyl, benzyl or C_1-C_6 (monohalo or polyhalo)alkyl;

R_3 is hydrogen, α-hydroxy, α-methyl, β-methyl or α-$OCOR_2$ wherein R_2 is identical to R_2 as defined hereinabove;

R_4 is hydrogen or fluoro;

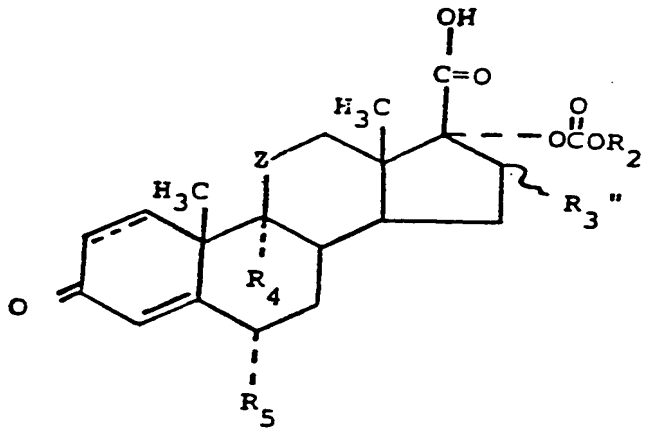
R_5 is hydrogen or fluoro;

X is -O-;

and the dotted line in ring A indicates that the 1,2-linkage is saturated or unsaturated;

(b) a quaternary ammonium salt of a compound of formula (I) wherein at least one of R_1 and R_2 is a halo-substituted alkyl group;

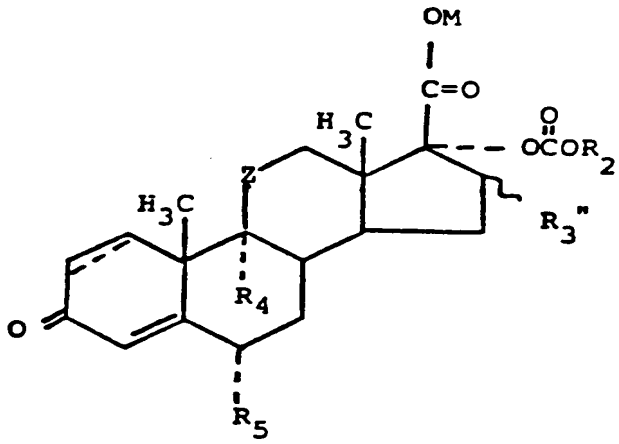
(c) a compound of the formula



(III)

wherein R_2, R_4, R_5 and the dotted line in ring A are as defined in (a) above, Z is carbonyl or β-hydroxymethylene and R_3" is hydrogen, α-methyl, β-methyl or α-$OCOR_2$ wherein R_2 is identical to R_2 above;

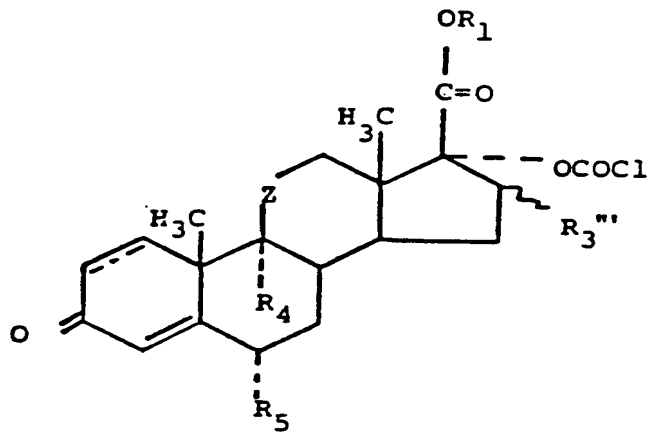
(d) a compound of the formula



(IV)

wherein M is alkali metal, thallium, alkaline earth metal/2 or NH_4 and R_2, R_3", R_4, R_5, Z and the dotted line in ring A are as defined in (a) and (c) above;

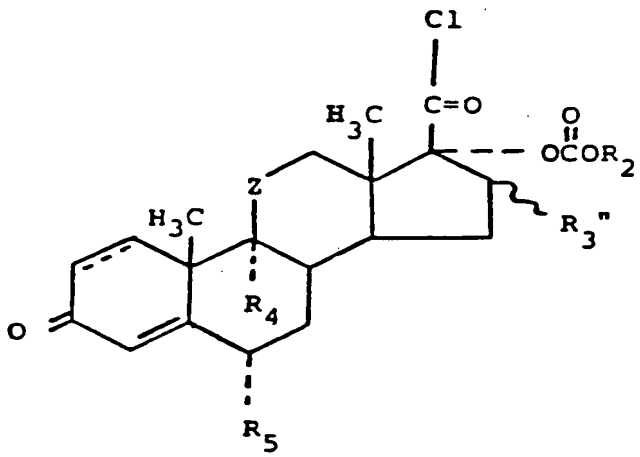
(e) a compound of the formula



(VII)

wherein R_3"' is hydrogen, α-methyl, β-methyl or α-OCOCl, and R_1, R_4, R_5, Z and the dotted line in ring A are as defined in (a) and (c) above;

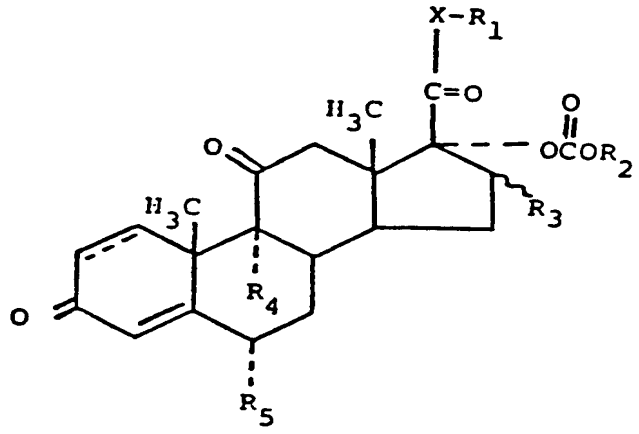
(f) a compound of the formula



(VIII)

wherein R_2, R_3", R_4, R_5, Z and the dotted line in ring A are as defined in (a) and (c) above; and

(g) a compound of the formula



(IX)

wherein R_1, R_2, R_3, R_4, R_5, X and the dotted line in ring A are as defined in (a) above.

3. A compound of Claim 1 or 2, said compound having the structural formula (I).

4. A compound of Claim 1 or 2, said compound being a quaternary ammonium salt of a compound of formula (I) wherein at least one of R_1 and R_2 is a halo-substituted alkyl group.

5. A compound of Claim 1 or 2, said compound having the structural formula (III).

6. A compound of Claim 1 or 2, said compound having the structural formula (IV).

7. A compound of Claim 1 or 2, said compound having the structural formula (VII).

8. A compound of Claim 1 or 2, said compound having the structural formula (VIII).

9. A compound of Claim 1 or 2, said compound having the structural formula (IX).

10. A compound of Claim 1, said compound having the structural formula (I) wherein R_3 is hydrogen, α-methyl, β-methyl, $=CH_2$ or α- or β-$O\overset{O}{\overset{\|}{C}}OR_2$.

11. A compound of Claim 1 or 2, said compound having the structural formula (I) wherein R_1 is C_1-C_6 alkyl.

12. A compound of Claim 1 or 2, said compound having the structural formula (I) wherein R_1 is C_1-C_6 (monohalo or polyhalo)alkyl.

13. A compound of Claim 12 wherein C_1-C_6 (monohalo or polyhalo)alkyl is C_1-C_6 monohaloalkyl.

14. A compound of Claim 13 wherein C_1-C_6 monohaloalkyl is C_1-C_6 monochloroalkyl.

15. A compound of Claim 14 wherein C_1-C_6 monochloroalkyl is chloromethyl.

16. A compound of Claim 11 wherein R_2 is C_1-C_6 alkyl or C_1-C_6 monohaloalkyl.

17. A compound of Claim 12 wherein R_2 is C_1-C_6 alkyl.

18. A compound of Claim 13 wherein R_2 is C_1-C_6 alkyl.

19. A compound of Claim 14 wherein R_2 is C_1-C_6 alkyl.

20. A compound of Claim 15 wherein R_2 is C_1-C_6 alkyl.

21. A compound of Claim 11 wherein R_2 is C_3-C_8 cycloalkyl, phenyl, benzyl or C_1-C_6 (monohalo or polyhalo)alkyl.

22. A compound of Claim 12 wherein R_2 is C_3-C_8 cycloalkyl, phenyl, benzyl or C_1-C_6 (monohalo or polyhalo)alkyl.

23. A compound of Claim 13 wherein R_2 is C_3-C_8 cycloalkyl, phenyl, benzyl or C_1-C_6 (monohalo or polyhalo)alkyl.

24. A compound of Claim 14 wherein R_2 is C_3-C_8 cycloalkyl, phenyl, benzyl or C_1-C_6 (monohalo or polyhalo)alkyl.

25. A compound of Claim 15 wherein R_2 is C_3-C_8 cycloalkyl, phenyl, benzyl or C_1-C_6 (monohalo or polyhalo)alkyl.

26. A compound of Claim 1, said compound having the structural formula (I) wherein X is -O-.

27. A compound of Claim 12 wherein X is -O-.

28. A compound of Claim 13 wherein X is -O-.

29. A compound of Claim 14 wherein X is -O-.

30. A compound of Claim 17 wherein R_4 and R_5 are hydrogen.

31. A compound of Claim 18 wherein R_4 and R_5 are hydrogen.

32. A compound of Claim 19 wherein R_4 and R_5 are hydrogen.

33. A compound of Claim 20 wherein R_4 and R_5 are hydrogen.

34. A compound of Claim 17 wherein at least one of R_4 and R_5 is fluoro.

35. A compound of Claim 18 wherein at least one of R_4 and R_5 is fluoro.

36. A compound of Claim 19 wherein at least one of R_4 and R_5 is fluoro.

37. A compound of Claim 20 wherein at least one of R_4 and R_5 is fluoro.

38. A compound of Claim 17 wherein R_4 is fluoro and R_5 is hydrogen.

39. A compound of Claim 18 wherein R_4 is fluoro and R_5 is hydrogen.

40. A compound of Claim 19 wherein R_4 is fluoro and R_5 is hydrogen.

41. A compound of Claim 20 wherein R_4 is fluoro and R_5 is hydrogen.

42. A compound of Claim 35 wherein R_3 is α-methyl or β-methyl.

43. A compound of Claim 37 wherein R_3 is α-methyl or β-methyl.

44. A compound of Claim 39 wherein R_3 is α-methyl or β-methyl.

45. A compound of Claim 41 wherein R_3 is α-methyl or β-methyl.

46. A compound of Claim 1 or 2, said compound having the structural formula (I) wherein R_1 is $-CH_2COOR_6$, $-CH_2-Y-(C_1-C_6$ alkyl) or $-CH_2-O\overset{O}{\overset{\|}{C}}R_6'$.

47. A compound of Claim 1, said compound having the structural formula (I) wherein R_1 is $-CH_2CONR_7R_8$.

48. A compound of Claim 47 wherein at least one of R_7 and R_8 is hydrogen or C_1-C_6 alkyl.

49. A compound of Claim 47 wherein R_7 and R_8 are combined so that $-NR_7R_8$ represents the residue of a saturated monocyclic secondary amine containing 5 to 7 carbon atoms.

50. A compound of Claim 49 wherein $-NR_7R_8$ represents morpholino, 1-pyrrolidinyl, 4-benzyl-1-piperazinyl, perhydro-1,2,4-oxathiazin-4-yl, 1- or 4-piperazinyl, 4-methyl-1-piperazinyl, piperidino, hexamethyleneimino, 4-phenylpiperidino, 2-methyl-1-pyrazolidinyl, 1- or 2-pyrazolidinyl, 3-methyl-1-imidazolidinyl, 1- or 3-imidazolidinyl, 4-benzylpiperidino or 4-phenyl-1-piperazinyl.

51. A compound of Claim 1, said compound having the structural formula (I) wherein R_1 is $-\underset{R_9}{CH}-Y-$(lower alkyl) wherein R_9 is hydrogen or methyl, or wherein R_9 and the lower alkyl group adjacent to Y are combined so that R_1 is $-\underset{\text{alkylene}}{CH}-Y-$ wherein Y is -S-, -SO-, $-SO_2-$ or -O- and the alkylene group contains 3 to 10 carbon atoms, of which at least 3 and no more than 6 are ring atoms.

56. A compound of Claim 1 or 2, said compound having the structural formula (III) wherein Z is β-hydroxymethylene and R_2 is C_1-C_6 alkyl.

57. A compound of Claim 1 or 2, said compound having the structural formula (IV) wherein Z is β-hydroxymethylene and R_2 is C_1-C_6 alkyl.

58. A compound of Claim 1 or 2, said compound having the structural formula (VII) wherein Z is β-hydroxymethylene and R_1 is C_1-C_6 alkyl or C_1-C_6 monohaloalkyl.

59. A compound of Claim 1 or 2, said compound having the structural formula (VIII) wherein Z is β-hydroxymethylene and R_2 is C_1-C_6 alkyl.

60. A compound of Claim 1 or 2, said compound having the structural formula (IX) wherein R_1 is C_1-C_6 (monohalo or polyhalo)alkyl.

61. A compound of Claim 60 wherein C_1-C_6 (monohalo or polyhalo)alkyl is C_1-C_6 monohaloalkyl.

62. A compound of Claim 61 wherein R_2 is C_1-C_6 alkyl.

63. A compound of Claim 1 or 2, said compound having the structural formula (IX) wherein R_1 is C_1-C_6 alkyl or C_1-C_6 monohaloalkyl, R_2 is C_1-C_6 alkyl or C_1-C_6 monohaloalkyl and X is -O-.

65. A compound of Claim 2, said compound having the structural formula (IX) wherein R_1 is C_1-C_6 alkyl, $-CH_2COOR_6$, $-CH_2$-Y-(C_1-C_6 alkyl) or $-CH_2-O\overset{O}{\overset{\|}{C}}R_6'$.

66. The compound of Claim 2 which is chloromethyl 11β-hydroxy-17α-methoxycarbonyloxyandrost-4-en-3-one-17β-carboxylate.

67. The compound of Claim 2 which is chloromethyl 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate.

68. The compound of Claim 2 which is chloromethyl 17α-butoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate.

69. The compound of Claim 2 which is chloromethyl 11β-hydroxy-17α-isopropoxycarbonyloxyandrost-4-en-3-one-17β-carboxylate.

70. The compound of Claim 2 which is chloromethyl 17α-ethoxycarbonyloxy-9α-fluoro-11β-hydroxy-16β-methylandrosta-1,4-dien-3-one-17β-carboxylate.

71. The compound of Claim 2 which is chloromethyl 9α-fluoro-11β-hydroxy-16α-methyl-17α-propoxycarbonyloxyandrosta-1,4-dien-3-one-17β-carboxylate.

72. The compound of Claim 2 which is 1-chloroethyl 11β-hydroxy-17α-isopropoxycarbonyloxyandrost-4-en-3-one-17β-carboxylate.

73. The compound of Claim 2 which is 1-chloroethyl 9α-fluoro-11β-hydroxy-17α-isopropoxycarbonyloxy-16β-methylandrosta-1,4-dien-3-one-17β-carboxylate.

74. The compound of Claim 2 which is chloromethyl 17α-ethoxycarbonyloxy-11β-hydroxyandrosta-1,4-dien-3-one-17β-carboxylate.

75. The compound of Claim 2 which is chloromethyl 11β-hydroxy-17α-isopropoxycarbonyloxyandrosta-1,4-dien-3-one-17β-carboxylate.

76. The compound of Claim 2 which is chloromethyl 17α-ethoxycarbonyloxy-9α-fluoro-11β-hydroxyandrosta-1,4-dien-3-one-17β-carboxylate.

77. The compound of Claim 2 which is chloromethyl 17α-ethoxycarbonyloxy-9α-fluoro-11β-hydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate.

78. The compound of Claim 2 which is chloromethyl 9α-fluoro-11β-hydroxy-17α-isopropoxycarbonyloxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate.

79. The compound of Claim 2 which is chloromethyl 9α-fluoro-11β-hydroxy-17α-isopropoxycarbonyloxy-16β-methylandrosta-1,4-dien-3-one-17β-carboxylate.

80. The compound of Claim 2 which is chloromethyl 9α-fluoro-11β-hydroxy-17α-methoxycarbonyloxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate.

81. The compound of Claim 2 which is chloromethyl 9α-fluoro-11β-hydroxy-16α-methyl-17α-pentyloxycarbonyloxyandrosta-1,4-dien-3-one-17β-carboxylate.

82. The compound of Claim 2 which is fluoromethyl 17α-ethoxycarbonyloxy-9α-fluoro-11β-hydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate.

83. The compound of Claim 2 which is methyl 17α-(2-chloroethoxy)carbonyloxy-9α-fluoro-11β-hydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate.

84. The compound of Claim 2 which is 17α-ethoxycarbonyloxy-9α-fluoro-11β-hydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylic acid.

85. The compound of Claim 2 which is 9α-fluoro-11β-hydroxy-17α-isopropoxycarbonyloxy-16β-methylandrosta-1,4-dien-3-one-17β-carboxylic acid.

86. The compound of Claim 2 which is 9α-fluoro-11β-hydroxy-16α-methyl-17α-propoxycarbonyloxyandrosta-1,4-dien-3-one-17β-carboxylic acid.

87. The compound of Claim 2 which is 9α-fluoro-11β-hydroxy-17α-methoxycarbonyloxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylic acid.

88. The compound of Claim 2 which is 11β-hydroxy-17α-methoxycarbonyloxyandrost-4-en-3-one-17β-carboxylic acid, 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylic acid, 17α-butoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylic acid, or 11β-hydroxy-17α-isopropoxycarbonyloxyandrost-4-en-3-one-17β-carboxylic acid.

89. The compound of Claim 2 which is sodium 11β-hydroxy-17α-methoxycarbonyloxyandrost-4-en-3-one-17β-carboxylate, sodium 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate, sodium 17α-butoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate, or sodium 11β-hydroxy-17α-isopropoxycarbonyloxyandrost-4-en-3-one-17β-carboxylate.

90. The compound of Claim 2 which is chloromethyl 17α-chlorocarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate.

91. The compound of Claim 2 which is chloromethyl 17α-ethoxycarbonyloxy-9α-fluoro-16α-methylandrosta-1,4-diene-3,11-dione-17β-carboxylate.

92. The compound of Claim 2 which is chloromethyl 9α-fluoro-17α-isopropoxycarbonyloxy-16β-methylandrosta-1,4-diene-3,11-dione-17β-carboxylate.

93. A pharmaceutical composition of matter comprising an anti-inflammatory effective amount of a compound of Claim 1 or 2 having the structural formula (I), in combination with a non-toxic pharmaceutically acceptable carrier therefor suitable for topical or other local application.

94. A method for alleviating inflammation in or on a warm-blooded animal exhibiting a topical inflammatory response, which comprises topically administering thereto an anti-inflammatory effective amount of a composition of Claim 93.

95. A method for alleviating inflammation in or on a warm-blooded animal exhibiting a localized inflammatory response, which comprises locally administering thereto an anti-inflammatory effective amount of a composition of Claim 93.

96. A compound of Claim 13 wherein C_1-C_6 monohaloalkyl is C_1-C_6 monofluoroalkyl.

97. A compound of Claim 96 wherein C_1-C_6 monofluoroalkyl is fluoromethyl.

98. A compound of Claim 96 wherein R_2 is C_1-C_6 alkyl.

99. A compound of Claim 97 wherein R_2 is C_1-C_6 alkyl.

100. A compound of Claim 96 wherein X is -O-.

101. A compound of Claim 100 wherein R_4 and R_5 are hydrogen.

102. A compound of Claim 101 wherein R_3 is hydrogen.

103. A compound of Claim 100 wherein at least one of R_4 and R_5 is fluoro.

104. A compound of Claim 100 wherein R_4 is fluoro and R_5 is hydrogen.

105. A compound of Claim 104 wherein R_3 is α-methyl or β-methyl.

106. The compound of Claim 2 which is fluoromethyl 11β-hydroxy-17α-isopropoxycarbonyloxyandrost-4-en-3-one-17β-carboxylate.

107. The compound of Claim 2 which is fluoromethyl 17α-ethoxycarbonyloxy-9α-fluoro-11β-hydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate.

108. The compound of Claim 2 which is fluoromethyl 9α-fluoro-11β-hydroxy-16α-methyl-17α-n-propoxycarbonyloxyandrosta-1,4-dien-3-one-17β-carboxylate.

109. A compound of Claim 1 or 2, said compound having the structural formula (I) wherein R_3, R_4 and R_5 are hydrogen and the 1,2 linkage is saturated or unsaturated.

110. A compound of Claim 1 or 2, said compound having the structrual formula (I) wherein R_3 is selected from hydrogen or methyl, R_4 is fluoro and R_5 is hydrogen and the 1,2 linkage is saturated or unsaturated.

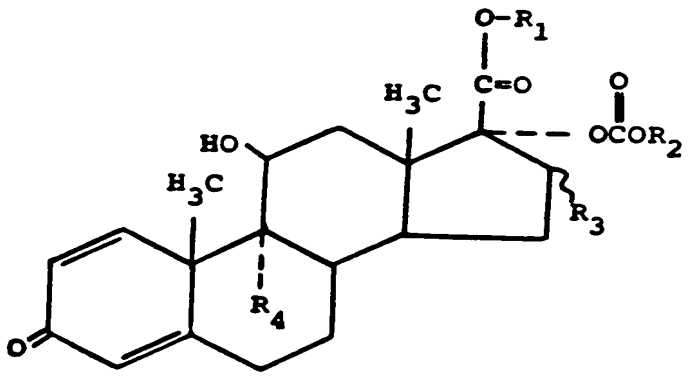
111. A compound of Claim 1 or 2, said compound having the structural formula (I) wherein R_3 is hydrogen or methyl, R_4 is hydrogen or fluoro and R_5 is fluoro or methyl and the 1,2 linkage is unsaturated.

112. A compound of Claim 1 or 2, said compound having the structural formula (I) wherein R_3 is α-$OC(=O)R_2$ and wherein R_4 is fluoro and R_5 is hydrogen and the 1,2 linkage is unsaturated.

113. A compound of Claim 63 wherein R_3 is hydrogen or methyl, R_4 is hydrogen and R_5 is hydrogen or chloro and the 1,2 linkage is saturated or unsaturated.

114. The compound of Claim 45 wherein R_3 is α-methyl and the 1,2 linkage is unsaturated.

115. A compound of the formula

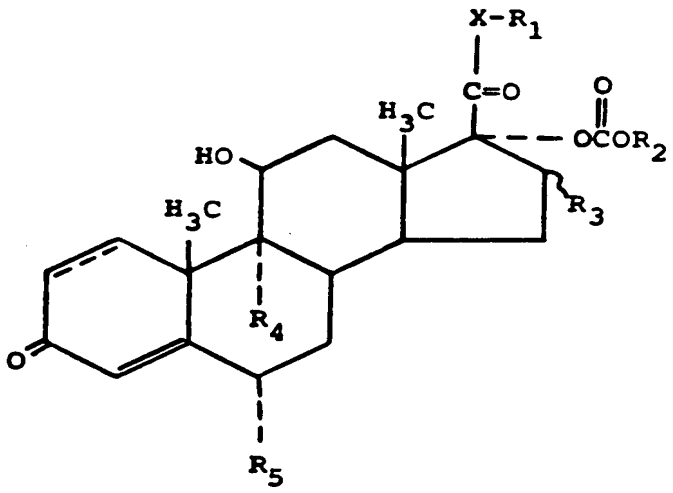


wherein R_1 is C_1-C_6 (monohalo)alkyl, R_2 is C_1-C_6 alkyl, R_3 is hydrogen, α-methyl or β-methyl and R_4 is hydrogen or fluoro.

116. A compound of Claim 115 wherein R_1 is chloromethyl.

117. A compound of Claim 115 wherein R_3 is α-methyl and R_4 is fluoro.

118. A compound of the formula



(I)

wherein:

R_1 is $-CH_2COOR_6$ wherein R_6 is C_1-C_6 alkyl; $-CH_2-Y-(C_1$-C_6 alkyl) wherein Y is -S-, -SO-, $-SO_2-$ or -O-; or $-CH_2O\overset{O}{\overset{\|}{C}}R_6'$ wherein R_6' is C_1-C_6 alkyl or phenyl;

R_2 is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, phenyl, benzyl or C_1-C_6 (monohalo or polyhalo)alkyl;

R_3 is hydrogen, α-hydroxy, α-methyl, β-methyl or α-$O\overset{O}{\overset{\|}{C}}R_2$ wherein R_2 is as defined above;

R_4 is hydrogen or fluoro;

R_5 is hydrogen or fluoro;

X is -O- or -S-;

and the dotted line in ring A indicates that the 1,2-linkage is saturated or unsaturated.

III. THE INVENTION:

The topic invention involves novel compounds which are consistent with Appellant's "soft drug" Approach.[1] Appellant's soft drug approach is a marked departure from traditional drug design based on structure/activity relationships, and emphasizes the factor of safety over that of intrinsic activity. Indeed, the ways in which the toxic dose of a target compound may be reduced depend upon the alteration of the disposition of the drug in the body. Thus, through the prodrug approach, the compound may be modified so that it is inactive of itself, but once it reaches its site of action, it becomes activated and produces its therapeutic effect. Hence, the distribution of the target compound is modified to reduce its undesired interaction with sites of action other than where it is wanted. The toxicity of the target compound may be divided into its intrinsic toxicity, which is related to its intrinsic activity, and the toxicities of its metabolites which may be inactive, active, or reactive. The toxicity of the inactive metabolite is, of course, zero, but those of the others are not. The toxicity of the active metabolites is of the same order as the intrinsic toxicity of the drug itself, but the pharmacokinetic distribution is different and therefore uncontrollable. The toxicity of the reactive metabolites is of a different order, and is the most important to avoid. Reactive metabolites are known to combine with DNA and other critical cellular macromolecules to produce mutations, cancer and cellular necrosis. Since reactive drug metabolites are

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[1] See pages 2 and 3, and the paragraph bridging pages 6 and 7, of Appellant's specification.

products of a reaction with enzymatically produced active oxygen, the avoidance of this route of metabolism will reduce a large portion of the toxicity of the lead compound.

The present invention, geared to specific derivatives, e.g., of hydrocortisone, features derivatizing known endogenous inactive metabolites of, e.g., hydrocortisone, for example, 11β, 17α-dihydroxy-androst-4-ene-17β-carboxylic acid, or cortienic acid, with metabolically labile biofunctional carbonate moieties. Such modification as to form a soft drug, which would have the same order of potency but a much lower order of toxicity, is a marked departure from use of ester groups (see the prior art) which have been shown to be effective in producing highly active compounds for dermal application (i.e., the antithesis of the "soft" drug approach).

Moreover, it too would have been expected by those skilled in this art that the simple 17β-esters would be subjected to intramolecular group transfer of the acyl moiety to the 17 -position, forming a reactive mixed anhydride species. This is precisely the situation that the soft drug approach seeks to avoid. The likely candidates for reaction with this type of reactive intermediate, the plasma proteins, would then be made immunogenic and cause unwanted side effects in such manner. The systemic lupus which is seen in some cases of hypercortisolism is, in fact, attributed to just such a mechanism. The cortisol is postulated to react with nucleophilic groups borne by the proteins.

Only Appellant has shown that this problem could be solved by the use of a 17α-alkyl carbonate in place of the 17α-acyl, in a 17β-ester steroidal basic nucleus. Likely

this is so because of the lower electrophilicity of the carbon in the carbonate, as opposed to the carbonyl carbon in the ester. A resonance interpretation makes this apparent.

And comparing the immediately aforesaid versus the carbonate and ester prior art, it is submitted that the claimed subject matter is manifestly patentable thereover.

IV. THE REFERENCES APPLIED IN THE FINAL REJECTION:

[i] Edwards, U.S. Patent No. 4,263,289, patented April 21, 1981 (hereinafter referred to as Edwards);

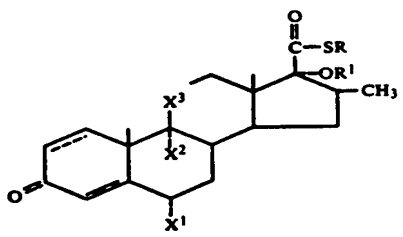
[ii] Phillips et al, U.S. Patent No. 3,856,828, patented December 24, 1974 (hereinafter referred to as Phillips (1));

[iii] Phillips et al, U.S. Patent No. 4,093,721, patented June 6, 1978 (hereinafter referred to as Phillips (2)); and

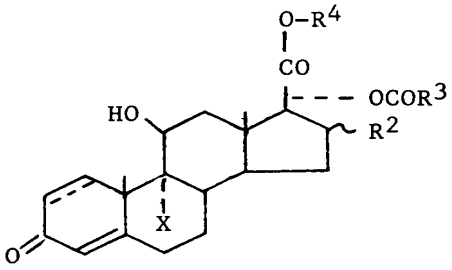
[iv] Sarett et al, U.S. Patent No. 3,558,675 (hereinafter referred to as Sarett).

V. DESCRIPTION OF THE INVENTION

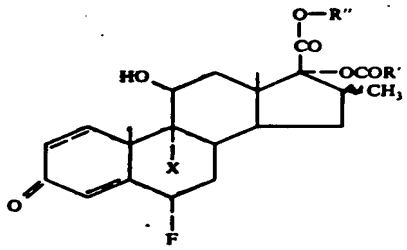
[i] Edwards discloses certain 16β-methyl-3-oxoandrost-4-ene and 16β-methyl-3-oxoandrosta-1,4-diene 17β-thiocarboxylic acid esters which are useful as anti-inflammatory steroids. One such compound is depicted below:



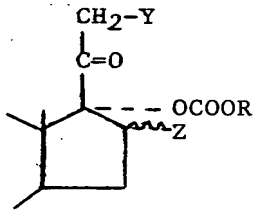
[ii] Phillips (1) discloses 17-beta-carboxylates and 17-alpha monoesters. The claimed compound is set forth below:



[iii] Phillips (2) also discloses 17-beta-carboxylates and 17-alpha monoesters. The claimed compound is set forth below:



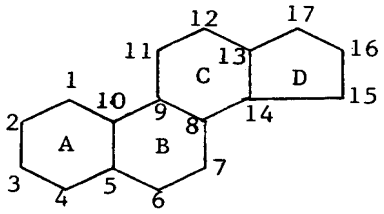
[iv] Sarett specifically pertains to saturated and unsaturated pregnane series steroids comprising 17-alpha-hydroxy-20-keto-pregnane-17-(alkyl, aryl and aralkyl) carbonates. These carbonates are stated to be useful as progestational agents which are valuable as esterus regulating agents. Ring D of the steroid nucleus is set forth below:



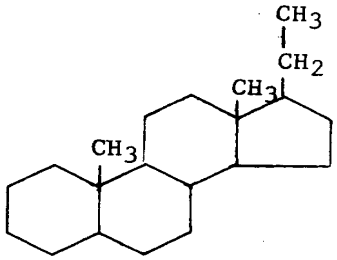
VI. STEROID CHEMISTRY DEFINITIONS:

[i] Steroid Ring Identification -

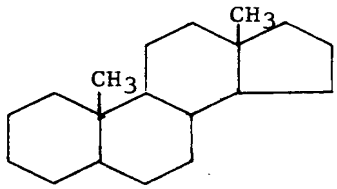
The Cyclopentanoperhydrophenanthrene Ring:



[ii] Pregnane Structure:



[iii] Andrastane Structure:



VII. THE ACTION APPEALED FROM:

In the Final Rejection dated November 24, 1987, the Examiner maintained the rejection of claims 1-45, 56-63 and 65-117, as follows:[2]

> Claims 1-45, 56-63 and 65-117 are rejected under 35 U.S.C. 103 as being unpatentable over the references of Phillipps et al (1 and 2) and Edwards in combination with Sarrett et al for

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[2] Claims 46-51 have only been objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and intervening claims. Claim 118 has been recognized as allowable.

reasons already of record. Applicant's arguments have been considered but are not seen as persuasive. Arguments presented in relation to the patents of Stache et al (4,242,334 and 4,377,575) are deemed irrelevant as such art [is] not part of the basis of the instant rejection. The Nakagawa declaration is noted but is not in point as it fails to address the expected utility of compounds produced as a result of the combination of the cited references.

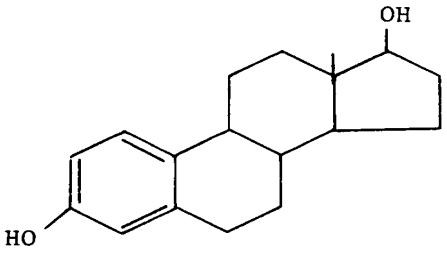
Further, after reviewing Appellant's response to the foregoing Official Action, the Examiner included the following comment in the Advisory Action mailed May 31, 1988:

> The rejection of claims 1-45, 56-63 and 65-117 is maintained for reasons of record. The Examiner does not concur with Appellant's narrow interpretation of the patent of Sarett et al. Allegations that the file history of the Sarett et al. patent is limited to a narrow genus of steroids is unique. Note that claim 1 as originally filed in application 842,788 as well as that of parent application 620,656 was directed to steroids in general. The opening statement in the patent of Sarett et al. was not provided for guidance but rather for teaching. During the mentioned interview, no agreement regarding allowability was made.

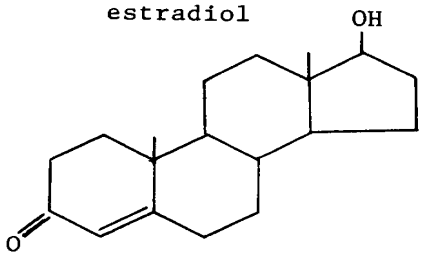
"UNTRUE" WAS THE TERM USED. NOTE PAPER #17

VIII. ARGUMENTS AND AUTHORITIES:

At the outset, Appellant would like to point out the unpredictable nature of this art, i.e., the art of steroid chemistry. All of steroid chemistry is based on a cyclopentanoperhydrophenanthrene ring; however, the various substituents which may be placed on that ring oftentimes provide very different physiological properties. Perhaps one of the more interesting examples of this phenomenon is best exemplified by the following two compounds:



estradiol



testosterone

The ovary is the principal site of extradiol production. Extradiol is an estrogen. Testosterone, on the other hand, is the principal circulating androgen and is secreted by the testes. These compounds while apparently quite similar in chemical structure possess very different physiological properties. Thus, what appear to be minor chemical changes on the cyclopentanoperhydrophenanthrene ring can lead to a very different effect. Appellant's invention should be considered in light of that this background.

To further reinforce the low level of predictability in this art, Appellant had also provided various pages from the book "Steroid Drugs" by Norman Applezweig in the response filed May 24, 1988. The highlighted sections on page 3 of the introduction show that minor variations in the steroid molecule can provide tremendously different properties. Further, Chapter 5, which begins on page 87, illustrates the extreme differences between progestogens and corticoids. These differences further distinguish the teachings of the various prior art references and leave serious doubt whether it even makes

VARIATIONS ON D RING TYPICALLY AFFECT RELATIVE ACTIVITY - NOT TYPE OF ACTIVITY

sense to combine the references in the manner set forth in the Final Rejection.

Appellant maintains that the true scope and content of the prior art, the differences between the claimed invention and such prior art, and the level of ordinary skill in this art, have yet to be definitively addressed.

At the outset it should be recognized that the primary focus of Appellant's invention is relative to the 17-alpha and 17-beta positions of the androstane molecule and variations of substituents at the 17-alpha and 17-beta positions (along with the 6, 9 and 16 positions of the steroid nucleus) which account for the extraordinary dose related anti-inflammatory activity of the compounds claimed herein while at the same time minimizing systemic glucocorticoid effects. The prior art does not recognize or even come close to recognizing the importance of certain substituents at these positions.

A cursory review of the references indicates that Phillips (1) and (2) as well as Edwards discloses steroids of the androstane series which have 17-beta carboxylate and 17-alpha-hydroxy (acyloxy) group which possess anti-inflammatory activity. The secondary reference, Sarett, discloses 17-alkoxy-carboxyloxy pregnane steroids. It would not be obvious for one of ordinary skill in the art to substitute the 17-carbonate ester of Sarett for the 17-esters of Phillips (1) and (2) or Edwards.

Each reference will now be discussed in greater detail. Phillips (1) and (2) disclose 17-beta-carboxylates and 17-alpha monoesters, i.e., by definition 17-alpha-acyloxy groups. More particularly, the Phillips references teach

$-\overset{O}{\overset{\|}{C}}-OR''$ (or R^4) substituents at the 17-beta position in which R" or R^4 represent halogen substituted C_1-C_3 alkyl groups and 17-alpha-substituents represented by $-O\overset{O}{\overset{\|}{C}}R'$ (or R^3) wherein R^3 is hydrogen, alkyl or phenyl. There is no disclosure in the Phillips references of a hydroxy (acyloxy) moiety at the 17-alpha position. Of greater significance is the fact that the Phillipps references do not suggest the carbonate ester type derivatives presently claimed herein where the 17-alpha position is substituted by a moiety represented by the formula $-O\overset{O}{\overset{\|}{C}}-OR_2$, which corresponds by definition to a substituted oxycarbonyloxy moiety.

Edwards discloses anti-inflammatory agents of the androstane series, similar to Phillipps (1) and (2), except that the 17-beta-carboxylate substituents comprise thiocarboxylates. Again, there is no suggestion of any substituent resembling Appellant's claimed 17-alpha-oxycarbonyloxy compounds. Edwards discloses a $-OR^1$ substituent at the 17-alpha position in which R^1 is hydrogen or alkanoyl. Therefore, like Phillipps (1) and (2), Edwards discloses acyloxy substituents, i.e., acetyl, propionyl, butyryl, etc., monoester substituents, etc., and not carbonate esters. Recognizing these deficiencies of the primary references, the Examiner has relied on Sarett which possess a 17-alpha-carbonate substituent in order to suggest that it would have been obvious at the time of Appellant's invention to design an anti-inflammatorily active steroid bearing an oxy-carbonyloxy substituent at the 17-alpha

position of the steroid nucleus. It is respectfully submitted that one of ordinary skill in the art at the time of Appellant's invention would in no way consider the Sarett reference pertinent to the design of an extremely potent anti-inflammatory glucocorticosteroid and, therefore, whatever the Sarett reference teaches with respect to 17-alpha substituents is totally irrelevant to both the disclosures of the primary references as well as Appellant's claimed invention. In this regard, the Examiner's attention is respectfully directed to the fact that the Sarett reference pertains to saturated and unsaturated pregnane series steroids comprising 17-alpha-hydroxy-20-keto-pregnane-17-(alkyl, aryl and aralkyl) carbonates having disclosed utility only as progestational agents valuable as esterus regulating agents. The primary reference relied upon by the Examiner and the presently claimed invention pertain specifically to androstane type steroids possessing specific anti-inflammatory activity, whereas the secondary reference to Sarett has nothing to do with anti-inflammatory steroid compounds, and it is, therefore, respectfully submitted that the Examiner's combination of Sarett with the primary references in an effort to modify the teachings of the primary references in an attempt to arrive at a formula structurally similar to the compounds claimed by Appellant represents an unreasonable basis of rejection on obviousness grounds under 35 U.S.C. §103. In order to render a claimed invention obvious within the meaning of §103, the prior art must contain some suggestion of the desirability and the manner of making the proposed modification. See, e.g., In re

Antonie, 195 U.S.P.Q. 6; In re Taborski, 183 U.S.P.Q. 50. No such suggestion is offered.

Before progressing any further, Appellant would like to address the scope of the disclosure of Sarett. Appellant maintains that Sarett only relates to 17-(alkyl, aryl and aralkyl)carbonate esters of 17-alpha-hydroxy-2-keto-steroids of the saturated and unsaturated pregnane series. Support for this can be found at column 1, lines 16-18, and throughout the specification and examples of Sarett. The Examiner, however, maintains that Sarett is not so limited and rather relates to all steroid carbonates. The only support for this position is the first sentence of the abstract which reads, "The invention disclosed herein is concerned generally with novel steroid carbonates and processes for preparing them."

Appellant maintains that the one isolated sentence selected by the Examiner from Sarett was only provided as guidance to describe in general terms the general category of the compounds disclosed by Sarett. That sentence is only a general statement of the field of the art and assists the U.S. Patent and Trademark Office in classification. The first sentence of the Abstract is not a teaching provided by Sarett.

Note that the second sentence more particularly characterizes what Sarett perceived to be his invention. Indeed, all other reference to steroids throughout the Sarett disclosure is specifically and exclusively directed to saturated and unsaturated 17-alpha-hydroxy-2-keto-pregnane-17-carbonates. Thus, no basis is provided for extending any

of the teachings of Sarett to Appellant's claimed androstane derivatives.

For further insight into what Sarett fairly discloses, Appellant provided a copy of the file history of Sarett as well as the parent application, U.S. Serial No. 620,656 filed March 6, 1967. Appellant would like to direct the Board's attention to the top half of page 3 of the Amendment filed October 31, 1968 in U.S. 620,656 wherein Sarett clearly characterized and limited their invention to "17-alpha-hydroxy steroid 17-carbonates". Sarett argued that their compounds were "clearly distinct from" the ester compounds known in the prior art at the time. This further supports and confirms Appellant's interpretation of Sarett.

However, the Examiner did not find the foregoing to be persuasive, and he emphasized in the Advisory Action that original claim 1 in U.S. Serial No. 842,788 as well as 620,606 was directed to steroids in general. The Examiner is correct in that the original claims appear to be directed to a broader class of steroids; however, there is absolutely no support in terms of a disclosure or any teaching for such a broad interpretation in either the specification or the examples. The first sentence in the Abstract of Sarett must be considered in the framework of the reference as a whole, and the Examiner cannot cite or refer to isolated sections of a patent in a vacuum. One isolated sentence cannot be pulled from the specification to expand the patent's teachings far beyond anything intended by the Applicants. There must be some direction or reason for making the specific selection of substituents espoused by the Examiner. Ex parte Kuhn (POBA 1961), 132 U.S.P.Q. 359. No motivation or suggestion let

alone a teaching is provided for combining the references in the manner taught by the Examiner.

While certainly not required as per In re Grunwell and Petrow, supra, but nevertheless to further highlight the non-obviousness of Appellant's invention, comparative data exist demonstrating the patentable non-obviousness of the claimed compounds versus the compounds of Phillipps (1) and (2), in the effects on granulation tissue formation and thymus weight caused by implantation of cotton pellets in rats.

Thus, Appellant provided a Declaration by Dr. Kazuyuki Nakagawa in his Reply filed September 29, 1986. As can be seen from Table 1 of the Declaration, the representative compounds of the two "primary" references effect significant decrease in the thymus weight, even at a very low dose of 10 or 30 μg/pellet.

On the other hand, the claimed compounds which correspond to the reference compounds tested in the Declaration do not effect such significant decrease in thymus weight at the same dosage level. Note the third compound in TABLE IV on page 41 of the Specification and the first compound in TABLE V-b on page 43 of the Specification.

In view of this, the two primary references, Phillips (1) and (2) do not teach the unexpectedly low levels of systemic side effects of the claimed compounds, and certainly do not render the claimed invention obvious.

At one point, the Examiner also alleged that Sarett teaches the "conventionality" of modifying a hydroxy substituent with oxycarbonyloxy substituents at the 17-alpha-

position of the steroid nucleus. Appellant categorically denies such a statement.

In the first place, it is not understood how only one reference can show the "conventionality" of the oxycarbonyloxy modification. Surely, it cannot be said that Sarett "teaches" such modification to be conventional.

Furthermore, as Appellant maintained above, Sarett is only concerned with a completely different class of compounds. The compounds disclosed in Sarett are saturated and unsaturated 17-alpha-hydroxy-20-keto-pregnane-17-carbonates which are markedly different from the claimed androstane derivatives, especially in the absence of a hydroxyl group at the 11-position and the presence of the group $-CO-CH_2-Y$ (Y=halo or H) at the 17-beta-position. Such pregnane derivatives, which are ketone derivatives, are wholly distinct from the claimed androstane derivatives which comprise an ester function (i.e., have a $-CO-O-R_1$ group at the 17-beta-position).

From the viewpoint of pharmaceutical activity, the compounds of Sarett are disclosed to have progestational activity and to be valuable as esterus regulating agents. See column 1, lines 24-27 of the '675 patent. Such pharmaceutical activity is not even remotely akin to the anti-inflammatory activity possessed by the compounds of Phillipps (1) and (2) and by the claimed compounds.

Therefore, one skilled in the art would not be motivated to modify the 17-alpha-position of the compounds of Phillipps (1) and (2) with an oxycarbonyloxy moiety. One skilled in the art could not predict what would happen when the alkanoyloxy group of the anti-inflammatory compounds of

Phillipps is modified by the oxycarbonyloxy group "suggested" by Sarett to be responsible for a completely different and irrelevant pharmaceutical activity.

Furthermore, Sarett does not at all teach that such oxycarbonyloxy modification will result in a marked improvement in anti-inflammatory activity and concomitant marked decrease in systemic side effects.

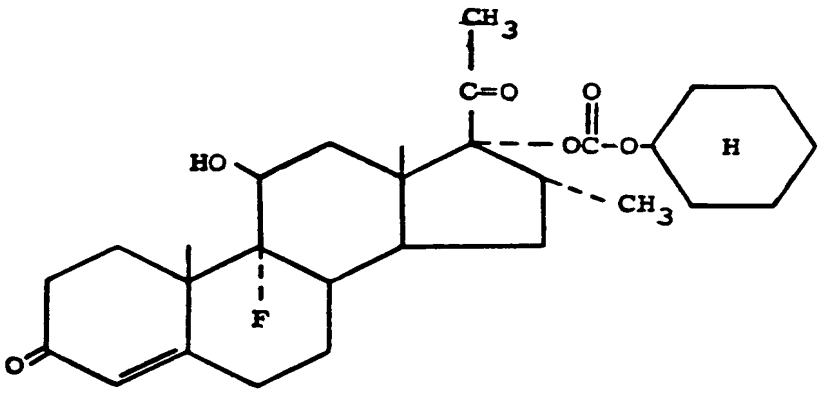
To add further support, see Experiment 2 of Dr. Nakagawa's Declaration discussed above. From Table 2 of the Declaration, it will be seen that replacement of the alkanoyloxy group of the compounds of Phillipps by the oxycarbonyloxy group results in marked increases in the therapeutic indices. The therapeutic index of the compound of Ex. 7A-3 is about 26 times higher than that of the corresponding compound of Phillipps, and the therapeutic index of the compound of Ex. 7A-12 is at least 10 times higher than that of the corresponding compound of Phillipps. This indicates that the oxycarbonyloxy replacement results in a significant increase in anti-inflammatory activity relative to lower systemic side effects. Such marked improvement is conspicuously absent from the teachings of Sarett and/or Phillipps (1) and (2).

Thus, not even a scintilla of evidence has been adduced supporting the proposition that Appellant's particular steroidal mixed esters/carbonates would even be prima facie obvious. In re Grabiak, 226 U.S.P.Q. 870; In re Grunwell and Petrow, supra.

Appellant has gone even further to support his position. Once again, such comparative evidence not being required but merely acting as additional icing on the cake.

A second Declaration by Dr. Kazuyuki Nakagawa was provided in Appellant's Response filed September 2, 1987, specifically comparing a broad spectrum of prior art compounds.

Sarett discloses at columns 2 and 3 a compound designated 9-alpha-fluoro-11-beta,17-alpha-dihydroxy-16-alpha-methyl-pregnane-4-ene-3,20-dione 17-cyclohexyl carbonate which is represented by the formula



Dr. Nakagawa has compared this type of compound taught by Sarett with a claimed compound. Compound (C) shown on page 3 of the second Nakagawa Declaration was selected as a representative compound per Sarett. The claimed compound compared with Compound (C) above was Compound (A), also shown on page 3 of the second Nakagawa Declaration. Compound (A) and Compound (C) have identical substituents on the corresponding positions, except for the 17-beta-position. That is to say, Compound (C) of Sarett has an ether group $-CO-CH_2Y$ at the 17-beta-position, whereas Compound (A) of the invention has an ester group $-CO-O-R_1$ at the same position.

However, Compounds (A) and (C) have identical substituents at the other corresponding positions.

Furthermore, Compound (A) of the claimed invention was compared with a compound described by Phillipps (1) and (2), i.e., Compound (B) shown on page 3 of the second Nakagawa Declaration. Compound (B) of Phillips and Compound (A) of the invention have identical substituents on corresponding positions, except for the 17-alpha-position (at which Compound (B) has a $-OCOR^3$ group, whereas Compound (A) of the invention has a carbonate group $-OCOOR_2$).

Thus, the claimed compounds have a carbonate group $-OCOOR_2$ per Sarett at the 17-alpha-position and an ester group $-CO-OR_1$ per Phillipps at the 17-beta-position. Such specific combination of 17-position substituents has been determined to be very important for achieving high anti-inflammatory activity, while at the same time reducing toxicity/undesirable side effects.

As will be seen from Table A on page 4 of the second Nakagawa Declaration, Compound (A) according to the invention has an unexpectedly <u>higher therapeutic index</u> compared with Compounds (B) and (C).

Table B on page 5 of the second Nakagawa Declaration reflects that the compound of the invention which has a $-OCO_2C_5H_{11}$ group at the 17-alpha-position, i.e., Compound (D) shown on page 5 thereof, also has a <u>high therapeutic index</u> compared with Compound (B).

Such an excellent therapeutic advantage imparted by the <u>specific combination</u> of the 17-position substituents according to the present invention is not evenly remotely

akin to any concept disclosed or suggested by Sarett, Phillips or Edwards.

In one Official Action, it was stated that Sarett teaches that modification at the 16 and 17-position substituents produces compounds with high activity. Such teaching, however, is in fact conspicuously absent from Sarett. Sarett merely suggests that certain steroidal carbonates have progestational activity and are useful as esterus regulating agents. Such utility is profoundly remote from the anti-inflammatory activity possessed by Appellant's claimed compounds. Sarett is totally silent as regards anti-inflammatory activity and low toxicity or side effects that characterize the claimed compounds, and does not even allude to modification of the 17-position substituents with a view towards improving anti-inflammatory activity and at the same time lowering the side effects, i.e., for improving therapeutic index.

As is apparent from the test results relative to the Compound (C), merely having a carbonate group ($-OCOOR_2$) at the 17-alpha-position (per Sarett) does not provide an unexpectedly high therapeutic index. Similarly, as seen from the test results relative to the Compound (B), merely having an ester group ($-CO-OR_1$) at the 17-beta-position (per Phillipps) also does not provide an unexpectedly high therapeutic index. Only when an ester group ($-CO-OR_1$) is present at the 17-beta-position and a carbonate group ($-OCOOR_2$) is simultaneously present at the 17-alpha-position, will the resulting compounds display unexpectedly high therapeutic indices. These unexpected results are a marked departure from the state of this art. The claimed compounds

profoundly differ from those of the prior art, exhibit therapeutic indices which could not be predicted therefrom, and are consummately patentable thereover.

Appellant emphasizes, however, that the aforediscussed evidence of surprising and/or unexpected results is in reality an aside. It truly is unessential for a conclusion of non-obviousness on this record. In plain terms, the combination of references upon which the Examiner's §103 rejection is based, cannot be justified. There exists no logical reason apparent from positive, concrete evidence of record which justifies combining references featuring anti-inflammatory steroids with a reference featuring compounds having progestational activity that are valuable as esterus regulating agents. In re Stemniski, 170 U.S.P.Q. 343; In re Regel, Buchel & Plempel, 188 U.S.P.Q. 136. The prior art is itself sorely lacking in any suggestion whatsoever that the combination postulated by the Examiner would either be desirable or operative. In re Imperator, 179 U.S.P.Q. 730; In re Gruskin, 110 U.S.P.Q. 288; Ex parte Walker, 135 U.S.P.Q. 195.

It is submitted that only Appellant's specification suggests any reason for combining the teachings of the prior art, but use of such suggestion is, of course, improper under the mandate of 35 U.S.C. §103. In re Shaffer, 108 U.S.P.Q. 326; In re Pye, 148 U.S.P.Q. 426; In re Wesslau, 147 U.S.P.Q. 391.

The prior art, in sum, contains absolutely no motivation to make Appellant's claimed compounds. In re Taborsky, 183 U.S.P.Q. 50.

While not necessary, to further reinforce and highlight the novelty of Appellant's invention, Appellant had brought U.S. Patent Nos. 4,242,334 and 4,377,575, both to Stache et al, to the Examiner's attention in the Reply filed September 29, 1986.

The '334 patent relates to certain corticoid 17-(alkyl carbonates) necessarily comprising, e.g., a reverse ester function, bonded strictly to a methylene bridge depending from a 20-keto group. The '575 patent features related corticoid 17-(alkyl carbonates), but wherein the methylene moiety is a terminal group, not a bridge, and is necessarily halogenated.

More importantly, though, it is submitted that these anti-inflammatory "carbonate" patents themselves point to, rather than detract from, the non-obviousness and hence patentability of the instantly claimed compounds, and clearly establish that the prior art steroidal esters and carbonates are not equivalent. Especially note the "steroids" case of In re Grunwell and Petrow, 203 U.S.P.Q. 1055.

Consider first that the file history of the '575 Stache et al patent itself demonstrates that the corticoid carbonates and esters are not equivalent. A copy of this Serial No. 216,258 file history was previously provided to the Examiner, especially the Stache et al Responses, and the Alpermann Declaration evidencing that indeed the carbonates and esters are not equivalent per In re Grunwell and Petrow, supra.

It too will be appreciated that the Stache et al carbonates actually teach away from Appellant's specific 17-alpha-carbonate-17-beta-carboxylates. The Stache et al

compounds, as aforesaid, necessarily comprise a halogenated methyl group, or a methylene bridge at the 21-position. In fact, in the file history of the '334 patent (previously provided to the Examiner), it is explicitly recognized that 17-carbonate-21-hydroxy compounds (more akin to those of Appellant) are unstable. Appellant's specific carbonates, however, are not only stable, but are even more stable than the carboxylates. Further, the inactive metabolites of Appellant's claimed compounds are themselves more stable than the metabolites of the carboxylates. Also consider that the Stache et al metabolites are active (or do not form metabolites and, hence, remain active), rather than inactive. Inactive metabolites, to reiterate, are the very prerequisite of a soft drug, a concept conspicuously alien to the prior art.

One should not lose sight of the fact that prior art discussed during prosecution of the Stache et al applications was judged and found infirm vis-a-vis the carbonates, whether singly or in any possible combination. See the file histories.

In summary, based upon the foregoing complete review of the respective teachings of the references relied upon by the Examiner, it is respectfully submitted that there is no disclosure, teaching or art suggested modification of the prior art compounds which would render Appellant's claimed compounds bearing novel 17-alpha-oxycarbonyloxy and 17-beta-carboxylate (or thiocarboxylate) substituents thereon in any sense obvious within the meaning of 35 U.S.C. §103.

IX. CONCLUSION:

From the foregoing, it is submitted that the factual and legal bases upon which the Examiner's §103 Final Rejections are grounded are more illusory than real and that said Final Rejections manifestly are untenable and ought to be reversed.

Respectfully submitted,

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